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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/010,081
Filing Date: November 09, 2001
Appellant(s): TRONO ET AL.

For Appellant

Supplemental
EXAMINER'S ANSWER

This is in response to the appeal brief filed 07/17/06 appealing from the Office action mailed 12/01/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The evidence relied upon by the examiner in the rejection of the claims under appeal is the following references of record:

- Zufferey et al, J. Virol. 72912):9873-9880, 1998
- Deisseroth, Clinical Cancer Research 5:1607-1609, 1999
- Chang et al, Gene Therapy 6:715-728, 1999
- Zufferey et al, J. Virol. 73(4):2886-2892, 1999
- Case et al, PNAS 96:2988-2993, 1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Double Patenting

Claims 4-5, 7-10, 12, 19, 22-23, 25, 30-34 and 38-45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-123 of copending Application No. 10/261,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of transduced host cells and the method of transducing human hematopoietic stem cells as claimed in the 10/261,078 encompasses the host cells and method of transducing human hematopoietic stem cells as claimed in instant application (10/010,081), for the same reasons of record as set forth in the office action mailed on 12/01/05

Claim Rejections - 35 USC § 103

A. Claims 4-5, 7-8, 12, 25, 30-34 and 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998 in view of Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999), for the same reasons of record as set forth in the office action mailed on 12/01/05.

Zufferey teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes (page 9873, abstract, col.2 para.1; page 9874, col.1 paras 3-7). The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR (page 9874, col.2 para.5, page 9875, table-1, page 9876, table-2, page 9877 table-3). The cited art further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable

transcription of a transgene in human hematopoietic progenitor cells upon transduction with a lentiviral vector (*see Case et al PNAS 96:2988-2993, 1999, ref. of record on PTO-1449*). In addition the cited art teaches transduction of human PBLs and human lymphocytic SupT1 cells using the SIN expression vector (page 9875, table-1; page 9878 fig-4). The cited art further teaches that inactivation of LTR provides higher signal to noise ratio which falls in the range of about 10 to about 200 (see page 9876 table 2).

Even though Zufferey teaches transduction of human PBLs the cited art does not teach the transduction of hematopoietic stem cell comprising a self-inactivating SIN-lentiviral vector wherein the transgene is a multidrug resistance gene (MDR).

Deisseroth teaches clinical trails involving multidrug resistance transcription units encoded in retroviral vectors. The cited art teaches the use of retroviral vectors to transfer human MDR-1 into human hematopoietic stem cells in-vitro (page 1607, col. 1 para 4; col. 2 para.2). The cited art further teaches clinical trials, which show engraftment of vector modified clonogenic hematopoietic progenitor cells into human patients (page 1608, col.1). The cited art further teaches the use of lentiviral vectors to transduce early hematopoietic stem cells, which resulted in the transduction of at least 80% of CD34+/CD38- hematopoietic stem cells (page 1608, col.2 para.d). In addition the cited art teaches o of clonal analysis (differentiation) of CD34+ CD38- transduced cells cultured in LTBMC culture media for long-term cultures (page 2889, col.2 para.5-6, page 2991, fig-3, page 2992 col.1).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zufferey by substituting the GFP reporter gene with a MDR gene and hematopoietic cells with hematopoietic stem cells in view of Deisseroth. It would have been further obvious to differentiate the transduced stem cell into different lineages, since hematopoietic stem cells have clonogenic potential. One would have been motivated to do so, since the transduction of human hematopoietic progenitor cells with the MDR-gene decrease the toxicity of

chemotherapeutic agents in hematopoietic cells and differentiated cells. One would have a reasonable expectation of success in doing so, since retrovirus induced transduction of human progenitor cells (to express a gene of interest) has been routine in the art at the time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

B. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Chang et al (Gene Therapy 6;715-728, 1999), for the same reasons of record as set forth in the office action mailed on 12/01/05.

As stated above the combined teaching of Zufferey and Deisseroth teaches transduciton of a human hematopoietic stem cell using self-inactivating HIV-1 based lentivirus vector (SIN). Even though Zufferey and Deisseroth teaches a hematopoietic stem cell transduced with self-inactivating HIV-1 based lentivirus vector, the cited art dose not teach a lentiviral vector, wherein the EF-1α promoter directs the expression of a transgene.

Regarding claims 9-10 specifically, Chang teaches a HIV-1 derived vector system comprising pTVΔEFGPF genetic construct, which comprises human eleongation factor 1α promoter (page 126, col.1 para.1, line 21-26). The cited art further teaches the transduction of human CD34+ hematopoietic stem cells using pTVΔEFGPF lentiviral vector, wherein the transduced progenitor cells express the GFP transgene under the control of the human eleongation factor 1α promoter (page 718. col.2 para. 2; pager 723, fig-5). Regarding claims 6-8 the cited art teaches that human hematopoietic progenitor cells express the the GFP transgene expression under the control of an EF-1α promoter, wherein the signal to noise ratio of the expressed GFP falls with the range of about 10 and about 200 (page 723, fig-5 see inset a-d). The cited art disclose that the phase

contrast microscopy reveled that the strength of GFP signal is significantly higher than the untransduced colony (inset-a, lower colony). Such a contrast certainly fall in the range of signal to noise ratio as claimed (between about 10 and about 200). The signal to noise ratio is an arbitrary value that not only depends upon the strength of transgene signal by is also a function of instrument sensitivity and settings. Therefore the cited art clearly teaches that the EF-1α promoter provides transgene expression with higher signal to noise ratio in human hematopoietic progenitor cells. In addition, the cited art clearly anticipate the invention as claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the self-inactivating HIV-1 based lentivirus vector of Zufferey by substituting the CMV promoter with human elongation factor 1α promoter for the transduction of human hematopoietic stem cells. One would have been motivated to do so because the EF-1α promoter is strong promoter to regulate the expression of a transgene in primary CD34+ hematopoietic stem cells. One would have a reasonable expectation of success of success in doing so, since substituting a promoter sequence with another and transduction of hematopoietic stem cells using a lentiviral vector has been routine in art at time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

C. Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Zufferey et al (J. Virol. 73(4):2886-2892, 1999, ref. of record on PTO-1449), for the same reasons of record as set forth in the office action mailed on 12/01/05.

As stated above the combined teaching of Zufferey and Deisseroth teaches transduciton of a human hematopoietic stem cell using self-inactivating HIV-1 based lentivirus vector (SIN). However Zufferey-1998 does not teach a SIN vector comprising the virus posttranscriptional regulatory element that promotes the expression of a transgene, wherein the posttranscriptional regulatory element is woodchuck hepatitis virus posttranscriptional regulatory element (WPRE).

Zufferey-1999 teaches a HIV-1 based retroviral vector (pHR' CMV-GFP) that contains woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). see page 2887 fig-1A, col.2 para. 2). The cited art further teaches that WPRE enhances the expression of a transgene in host cells transduced by the HIV-based vectors (page 2888, fig-2, col.2 results).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zefferey-1998 by incorporating posttranscriptional regulatory element obtained from woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) in view of Zufferey-1999. One would have been motivated to do so to increase the levels of expression of a transgene in host cells. One would have a reasonable expectation of success in doing so, since genetic modification of lentiviral vectors has been routine in the art at time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

(10) Response to Argument

The instant invention is drawn to a genetically modified human hematopoietic progenitor cell (and method of making the same) transduced with a self-inactivating lentiviral vector wherein the expression of a transgene is under the control of a promoter capable of expressing the transgene at signal-to-noise ratio of between about 10-200 in progenitor cells and differentiated hematopoietic cells.

The state of the art at the time the instant invention was such that genetic modification of human hematopoietic progenitor cell with lentiviral vectors has been routine in the art *(see Deisseroth et al, Exhibit 2, Case et al, Exhibit 5)*. In addition the genetic modification of lentiviral vectors, to make the vectors safe and efficient by inactivating LTRs and/or include tissue specific internal promoters has also been routine in the art at the time the instant invention was filed *(see Zufferey et al Exhibit 1 and 2, Chang et al Exhibit 3)*. In addition, the applicant has provided list of published articles that clearly reflects that the transduction of hematopoietic stem cells with variety of genetically modified lentiviral vector shad been routine in the art at the time the instant invention was filed *(see IDS PTO-1449 dated 06/18/04)*.

Obviousness-type double patenting *(Response to Argument)*

Claims 4-5, 7-10, 12, 19, 22-23, 25, 30-34 and 38-45 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-123 of copending Application No. 10/261,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of transduced host cells and the method of transducing human hematopoietic stem cells as claimed in the 10/261,078 encompasses the host cells and method of transducing human hematopoietic stem cells as claimed in instant application (10/010,081), for the same reasons of record as set forth in the office action mailed on 12/01/05

The applellants state that they will address the rejection should '078 case be allowed and should the allowed claims give rise to proper double-patenting rejection by filing a terminal disclaimer. The double patenting rejection is therefore maintained, since the instant application is not in condition of an allowance.

Claim Rejections - 35 USC § 103 *(Response to Argument)*

A. Claims 4-5, 7-8, 12, 25, 30-34 and 38-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998 in view of Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999).

Regarding the scope of the promoter, the applicant arguments revolves around the position taken that - *the CMV promoter is not a promoter of choice for use in the hemtopoeitic stem cells, and through the inclusion of the claim limitation "signal-to-noise ratio" the instant claims have been drafted to exclude the use of CMV promoter*. The applicant concludes that the combination of Zufferey I and Deissorth would be directed to use CMV promoter, which would not result in achieving the subject matter of either of claims 30 and 32 or claim depending thereform (see appeal brief pages 8-10).

However, this has been found not persuasive because the scope of the self-inactivating (SIN) recombinant lentiviral as claimed in the instant claims is not limited to a particular structure (i.e. a specific lentiviral vector design) and especially to a particular internal promoter [EMPHASIS ADDED], wherein the vector is capable of providing the asserted signal to noise ratio (see claims 30 and 32).

Furthermore, the "signal to noise ratio" is merely an "arbitrary value" that not only depends upon the choice of transgene and/or host cell, but is also upon the sensitivity of instrument and methodology used.

Zufferey I clealry teaches the use of a self-inactivating recombinant lentiviral vector containing an inactivated LTR and CMV or PGK promoter as an internal

promoter, which is all that is required to structurally meet the claim limitation of invention as claimed. In addition, the disclosed vector is capable of meeting the functional limitation (i.e. the asserted signal-to-noise ratio) for the reasons as set forth below.

The applicant fails to consider that the self-inactivating recombinant lentiviral vector contains an inactivated LTR and CMV promoter operably linked to a transgene, wherein the inactivation of LTR results in signal to noise ratio that falls well within the range of about 10 to about 200 (see Zufferey I page 9876, table 2). The cited art clearly teaches that the elimination of LTR-enhancer in the self-inactivating lentiviral vectors precludes the activation of a promoter located at a distance from the vector integration site (see Zufferey I, page 9877, col.2, see discussion para. 2). Besides CMV promoter the cited art also teaches that the incorporation of exogenous promoter of choice in the self-inactivating recombinant lentiviral vector has been routine in the art at the time the instant invention was filed (see Zufferey I page 9875. fig. 1; page 9876, fig-3). Therefore the teaching of cited art is not limited to the use of CMV promoter but encompasses variety of tissue specific promoters (i.e. PGK). Furthermore, the applicants argument that the recitation of "signal-to-noise ratio" in the claims 30 and 32 excludes the use of CMV promoter, has been found moot in view of fact that the elimination of LTR-enhancer in the self-inactivating lentiviral vectors precludes the activation of a promoter located at a distance from the vector integration site. Zufferey I has provide a clear evidcne that the inacivatin of LTR provides low background activity of a transgene operably linked t an internal promoter.

Regarding applicants argument that CMV is not a promoter of choice for use in in the hemtopoeitic progenitor cells, the applicants attention is drawn to supporting reference of record (Case et al, Exhibit 5) that clearly teaches that the CMV promoter when included in a lentiviral vector, is capable of promoting the expression of a trangene in CD34+ hematopoietic progenitor cells and differentiated cells. In addition the cited art teaches clonal analysis (i.e. differentiation) of CD34+ CD38- transduced cells cultured in LTBMC culture media to establish long-term cultures

which represent various lineages of hematopoietic system (see Case et al, page 2988, col.2 para 4, page. 2989, col.2 para. 3-5, fig-1, fig-3, table-1 table-2). Similarly, Deisseroth teaches clinical trails that employ lentivrial vectors encoding human MDR-1 gene and transduction of hematopoietic stem cells in-vitro (page 1607, col. 1 para 4; col. 2 para.2).

Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record. And one would have a reasonable expectation of success in doing so, since making SIN-lenitviral vectors with inactivated LTRs and a strong internal promoter; and the transduction of human progenitor cells with lentiviral vectors has been routine in the art at the instant invention was made.

Regarding claim 38, which is drawn to differentiation of hematopoietic cells into various lineages using a differentiation media, the applicant's attention is drawn to the fact that the scope of claim 38 encompasses any undefined culture media, which is capable of inducing differentiation. Deisseroth clearly teaches that incubation of hematopoietic progenitor cells in a medium supplemented with late acting growth factors, such as IL-3 in the presence of SCF has been shown to induce the maturation (i.e. differentiation) of stem cells page 1608, col.2 para.1, lines 3-5).

Regarding claims 39-45, which are drawn to differentiation of hematopoietic cells into various lineages using an undefined differentiation media, the applicant's attention is drawn to the fact that any culture medium that contains serum and/or supplemented with late acting growth factors, such as IL-3 in the presence of SCF has been shown to induce differentiation of stem cells into various lineages (see Deisseroth page 1608, col.2 para.1, lines 3-5). In addition, Case et al provides clear evidence that differentiation of hematopoietic stem cells can be achieved in long tem cultures (LTC) in the presence of growth factors which has also been described by Deissorth (see Case et al page 2989, col.2 para. 3-6, page 2992, col.1 para.3). Thus the cited art clearly teaches the limitation of claim 38 (differentiation media) and dependent claims, especially in view of the fact that the differentiation media (as claimed) has not been limited to a particular set of regents.

B. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Chang et al (Gene Therapy 6;715-728, 1999).

The applicant argues that it's their position that there is no motivation to combine the teachings of Chang with those of Zufferey I because there is no reasonable expectation that SIN design would work in Hematopoietic cells. The applicant further argues that behavior of internal promoters with respect to the LTR regions in the context of SIN design could not be predicted in advance.

However, this is found not persuasive because as stated above it is well established in the art at the time the instant invention was filed, that lentiviral vectors are capable of transducing the hematopoietic stem cells and the genetic modification of lentivrial vectors having inactivated LTR and/or an internal promoter of choice has been routine in the art. For example, Deissorth, Chang and Case provide clear evidence that the lentiviral vectors are capable of transducing the hematopoietic stem cells. Furthermore Zufferey I teaches that SIN-lentiviral vectors are capable of transducing non-dividing cells of hematopoietic system which includes the hematopoietic progenitor cells (see Zufferey I, page 9873, col.1 para.1).

The applicant's argument that the behavior of internal promoter with respect to LTR region in context to SIN design is considered unpredictable, has been found moot in view of Zufferey I, who clearly teaches that the incorporation of at least two different internal promoters in the SIN vector (see page 9877 and table-3). Contrary to applicant's assertion, Zufferey I clearly teaches that SIN design even prevents potential interference between the viral LTRs and the internal promoter which is considered most desirable implication in the field of gene therapy (see Zufferey I, page 9878, col.1 para. 2). Zufferey I further states that the comparison of various SIN and full length HIV vectors revealed some promoter and cell specific differences in the degree of promoter interference, but in all cases the magnitude of these effects was minimal (Zufferey I, page 9878, col.2, para 1, lines 5-8).

In addition the applicant fails to consider that Chang who teaches a lentiviral vector system comprising pTVΔEFGPF genetic construct, which contains human eleongation factor 1α promoter (EF1α) and transduction of human CD34+ hematopoietic using the lentiviral vector (see Chang page 726, col.1 para.1, line 21-26, page 718. col.2 para. 2; page 723, fig-5). The applicant fails to consider that Chang teaches the human hematopoietic progenitor cells expressing the GFP transgene under the control of an EF-1α promoter, wherein the signal to noise ratio of the expressed GFP falls with the range of about 10 and about 200 (page 723, fig-5 see inset a-d). Therefore the office ahs provided a clear evidence that EF-1α promoter is capable of regulating the expression of a transgene, which has been operably linked to it.

Thus the invention as claimed is prima facie obvious in view of combined teaching of cited prior art of record. And there exists a reasonable expectation of success, especially in view of the state of the art at the time of filing, which clearly teaches that the transduction of hematopoietic stem cells using lentiviral vectors and modification of letiviral vector having inactivated LTRs (SIN-vectors) and/or an internal promoter of choice (i.e. tissue specific promoter) has been routine in the art.

C. Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72912):9873-9880, 1998, ref. of record on PTO-1449) and Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999) as applied to claims 4-5, 7-8, 12, 25, 30-34 and 38-45 above, and further in view of Zufferey et al (J. Virol. 73(4):2886-2892, 1999, ref. of record on PTO-1449),

Regarding the current rejection the appellant merely argues to incorporate the arguments as set forth with respect of claim 30 from which claims 19, 22 and 23 depends.

However this found not persuasive for the reasons of record as set forth above with respect to claim 30. In addition the applicant fails to consider that Zufferey-1999 who clearly teaches a HIV-1 based lentiviral vector (pHR' CMV-GFP)

that contains woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). see page 2887 fig-1A, col.2 para. 2). Zufferey-1999 further teaches that WPRE enhances the expression of a transgene in host cells transduced by the HIV-based vectors (page 2888, fig-2, col.2 results). Therefor the cited art once again establishes that the genetic modification of lentiviral vectors to include varieties of internal regulatory elements has been routine in the art.

Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record. Again one would have a reasonable expectation of success in doing so, since genetic modification of lentiviral vectors that include substitution of internal promoters has been routine in the art at time the instant invention was made.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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